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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Enteric Neurons Get Our Undivided Attention

The enteric nervous system (ENS) is a network of neurons and glial cells interconnected in an intricate circuitry responsible for regulating the many aspects of gastrointestinal function essential for an organism's health and survival. Constructing that nervous system during embryogenesis is a developmental tour de force that relies on a highly coordinated process in which neural crest cells migrate within the gut wall, proliferating extensively along the way, to populate the gastrointestinal tract with the many subtypes of neurons and glia required to modulate gut motility, absorption, secretion, immunity, vasomotor tone, and microbiome composition. Understanding the fine details of how an enteric neuron knows when and where to stop migrating and settle down, what neurotransmitter profile it needs to express, and to which cellular targets its fibers should extend is a work in progress. But one thing that is well established is that this brain within our guts is remarkably complex. It thus came as a surprise when Kulkarni et al[1] suggested that nearly the entire ENS in healthy adult mice is replaced every 2 weeks. Their conclusion, based on compelling data, that at any given time the majority of myenteric neurons in the small intestine are less than 2 weeks old shook the ENS community. Not only did reconstructing the ENS every few weeks seem like a formidable task, but the finding contradicted several prior studies that showed essentially no ongoing neurogenesis in the uninjured, healthy adult intestine.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Virtanen et al[2] set out to replicate those results using the same methods as the original study. Adult mice were given the thymidine analogue, IdU, in their drinking water for 7 days at the same concentration and duration as Kulkarni et al.[1] Following an identical DNA denaturation procedure and using the same anti-BrdU antibody (with which IdU cross reacts), no IdU-immunoreactive myenteric neurons were detected in cryosections, paraffin sections, and wholemount preparations from the duodenum, jejunum, or ileum. This was confirmed in a second set of experiments following a 7-day course of EdU, again with no EdU/Hu double-reactive neurons seen. These results contrast sharply with those from Kulkarni et al,[1] who administered IdU for 1 week, followed by CIdU for a second week, and found that 88% of myenteric neurons in the ileum expressed 1 or both of these thymidine analogues, suggesting they had all been born during that 2-week period. Interestingly, despite this impressive rate of neuronal cell cycling, the total number of neurons did not change, consistent with the high rate of neuronal apoptosis they report in the same study.

So, is the adult ENS a stable population of enteric neurons content to live long, peaceful lives in the gut, or is it a highly dynamic and ever-changing population constantly turning over and establishing new synaptic connections? How do we reconcile these disparate images of the ENS? The former scenario of stability is easier to fathom, but more importantly is consistent with multiple published studies (all cited by Virtanen et al[2]) that show minimal neurogenesis in healthy adult intestine. It is unclear what factors contributed to Kulkarni et al's[1] result as compared with the other studies, but aside from potential methodologic issues, biologic variation and environmental factors could play a role. These include diet, gut microbes, differences in animal facility care, or even the time of day experiments were done. However, given the reproducible finding of limited enteric neuronal turnover, and Virtanen's inability to reproduce Kulkarni's results using very similar methodology, unless new evidence emerges, it seems likely that enteric neurons are a largely stable population.

Postnatal enteric neurogenesis has been observed during the first few months of life in rodents,[3,4] presumably to maintain neuronal density as the gut grows. The adult intestine is known to possess enteric neuronal progenitors, but aside from Kulkarni et al,[1] neurogenesis has only been reported following chemical denervation of the ENS[3] and in the setting of colitis.[5] Interestingly, in both of these injury models, the new neurons arose from enteric glial cells, and Belkind-Gerson et al[5] noted the absence of EdU incorporation in the colitis-associated newly born neurons, invoking a glia-to-neuron transition without DNA replication. The current study supports the idea that enteric neurons in the adult are not in constant turnover, but rather are a stable cell population ready to activate neuronal progenitors in response to specific stimuli. Many questions remain regarding enteric neurogenesis in the adult gut: what are the signals that activate it, which are the progenitor cells, what types of neurons can be generated, and how can this be leveraged for regenerative therapies to treat neurointestinal diseases? We are grateful to Virtanen et al,[2] Kulkarni et al,[1] and others who have contributed to this discussion and are leading us on a journey toward understanding this important aspect of gastrointestinal physiology.

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References

1. Kulkarni S, Micci MA, Leser J, Shin C, Tang SC, Fu YY, Liu L, Li Q, Saha M, Li C, Enikolopov G, Becker L,

Rakhilin N, Anderson M, Shen X, Dong X, Butte M, Song H, Southard-Smith EM, Kapur RP, Bogunovic M, Pasricha PJ. Adult enteric nervous system in health is maintained by a dynamic balance between neuronal apoptosis and neurogenesis. Proc Natl Acad Sci U S A 2017;114:E3709–E3718.

2. Virtanen H, Garton DR, Andressoo J-O. Myenteric neurons do not replicate in small intestine under normal, physiological conditions in adult mouse. Cell Mol Gastroenterol Hepatol 2022;14:27–34.
3. Laranjeira C, Sandgren K, Kessaris N, Richardson W, Ptocnik A, Vanden Berghe P, Pachnis V. Glial cells in the mouse enteric nervous system can undergo neurogenesis in response to injury. J Clin Invest 2011; 121:3412–3424.
4. Liu MT, Kuan YH, Wang J, Hen R, Gershon MD. 5-HT_4 receptor-mediated neuroprotection and neurogenesis in the enteric nervous system of adult mice. J Neurosci 2009;29:9683–9699.
5. Belkind-Gerson J, Graham HK, Reynolds J, Hotta R, Nagy N, Cheng L, Kamionek M, Shi HN, Aherne CM, Goldstein AM. Colitis promotes neuronal differentiation of Sox2+ and PLP1+ enteric cells. Sci Rep 2017; 7:2525.

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Conflicts of interest
The authors disclose no conflicts.


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